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Introduction: Biological Assessments in Female Reproductive Toxicology

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There are many components to reproductive health, including the development and maintenance of the reproductive tract; mature sexual appearance and behavior; adequate numbers of sound, viable germ cells; and a balanced neuroendocrine system. Thus, the range of processes for which biological markers might be developed is quite broad. In shaping a research program on markers, there are several distinctive features of female reproduction which merit consideration.

Distinctive Aspects of Female Reproductive Function

The female has a fixed store of germ cells, not readily accessible for study. In the female, germ cells undergo active mitosis early in the first trimester of development. By month 5 of gestation, the generation of new germ cells ceases, and at birth all of the existing pool—already substantially diminshed through the natural process of atresia—have entered meiosis. Shortly after birth, at metaphase of the first division, meiosis is suspended and only resumes at puberty when, under hormonal stimulation, one or two oocytes are recruited for ovulation. Thus, in contrast to the male of our species, gametogenesis in the female takes place mainly *in utero*, with a possible later period of oocyte vulnerability in the preovulatory phase of the cycle.

The relative lack of access to ovarian material, as compared with sperm and semen, has made it difficult to examine such issues as female germline exposure to toxins and possible oocyte killing or genetic damage. Recently, however, infertility patients, particularly those enrolled in IVF/ET (*in vitro* fertilization/embryo transfer) programs, have been a source of gonadal materials: in one instance, for a study of pollutant levels in follicular fluids (*1*) and in another for an estimate of oocyte chromosome anomalies (*2*). Such uses of IVF patients and materials could be very important in the development and validation of biological markers. An approach that is more amenable to application in broad population studies involves technology such as ultrasound, which, for example, might be useful in evaluating the oocyte stock.

A second distinct feature of female reproduction is a monthly cycle with marked endocrinologic fluctuations. Cycle length and regularity are indirect measures of ovulatory function, and a ready means to assess the influence of environmental exposures on reproductive capacity in nonconceptive women. Biological measures based on body temperature or on levels of steroid and gonadotropic hormones have the potential to provide an evaluation that is more precise, accurate, and informative than a menstrual history. Eventually such measures might become the counterpart to semen analysis in the male. The problem of cyclic fluctuations must be met, however, since serial sampling to obtain valid measurements is a difficult requirement in field applications.

A third distinctive aspect of female reproduction is the shorter, more circumscribed reproductive lifespan. Although both sexes may have a climacteric, only women experience menopause. The depletion of the oocyte stock with age is observed in many species, whereas aging effects on testicular function are subtle, variable, and uncertain. Since the postmenopausal state carries a raised risk for bone disorders (*3*), cardiovascular diseases (*4*), and other disorders, there are compelling reasons, even apart from fertility and sexuality, for wishing to extend the woman's reproductive lifespan.

Menopause (*5*), as well as pubertal onset (*6*), occurs differently in different times and places, suggesting environmental influences. Thus, development of markers for the milestones in a woman's reproductive life holds promise for toxicologic research.

Last, in our species the female provides the environment for implantation and embryonic development. Until very recently, the earliest recognition of a pregnancy was not at conception, or at implantation, but only at the time of the first missed period. In these circumstances, the true frequency and fate of human conception have eluded researchers; terms such as "clinically recognized pregnancy" have had to be invoked to indicate the limits on observed data.

One of the two papers that follow, by Robert Canfield

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and his colleagues, describes the development of a new assay of implantation, the most sensitive and specific test for pregnancy in the preclinical period that is currently available. Also discussed is the very rigorous field research by Allen Wilcox of the National Institute of Environmental Health Sciences, who has used the assay to generate the best estimates of early pregnancy loss currently available to us. This joint work stands as an exemplar of the development and validation of a biological marker, in any field.

The other paper in this section on female reproduction brings the perspective of the perinatal epidemiologist to a consideration of biological markers, citing general desiderata and circumstances under which such measures may strengthen epidemiologial strategies. The paper also proposes areas for biomarker development or refinement, based not only on what female reproductive processes it is possible to measure but also on processes that are likely to show effects of environmental exposures.

REFERENCES

1. Trapp, M., Baukloh, V., Bohnet, H-G., and Heeschen, W. Pollutants in follicular fluid. Fertil. Steril. 42: 146–148 (1984).
2. Wramsby, H., Fredga, K., and Liedholm, P. Chromosome analysis of human oocytes recovered from preovulatory follicles in stimulated cycles. N. Engl. J. Med. 316: 121–124 (1987).
3. Kelsey, J. L., and Hoffman, S. Risk factors for hip fracture. N. Engl. J. Med. 316: 404–406 (1987).
4. Bush, T. L., and Barrett-Connor, E. Noncontraceptive estrogen use and cardiovascular disease. Epidemiol. Rev. 7: 80–104 (1985).
5. Tanner, J. M. A History of the Study of Human Growth. Cambridge University Press, Cambridge, England, 1981.
6. Golub, S., Ed. Menarche. DC Heath, Lexington, MA, 1983.